Exhibit A

Foye's Principles of Medicinal Chemistry

Fifth Edition

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Regardless of the variations that may be undertaken in approaching natural products drug discovery, the process necessarily involves acquiring source materials, evaluating those materials for desirable biological activities, identifying the active constituent(s), optimizing lead compounds and developing drug candidates. A discussion of each of these processes is provided below.

Strategies and Approaches for Sourcing, Processing, and Archiving Natural Products for Drug Discovery

The goal of sourcing and sample acquisition is to obtain the maximum chemodiversity and therapeutically useful biological activity within the minimum number of collected samples. The goal of sample handling and preparation is to remove nuisance compounds that may interfere with bioassays in a nonspecific manner, to prepare the samples to be compatible with existing (and future) bioassays, and to store both the collected, unprocessed material and the processed samples in a manner that is easily retrievable and maximizes stability. Thus, the key decisions related to sourcing and sampling preparation are: what strategies to employ (including what sources on which to focus, i.e., plant, marine, microbial, insect, etc.), what quantity of specimen to collect, how to appropriately access and acquire specimens, how to store and process the collected samples, and how to handle and store the processed sample (usually extracts).

Sources of Natural Products

A number of strategies may be developed to select and acquire sources of natural products that are most likely to yield desirable compounds. Some strategies in use today include utilizing ethnobotanical and folklore information on medicinal plant use by specific cultures, exploring the relationship of genetic biodiversity and environmental factors to chemodiversity and specific biological activities, examining the chemical ecology of plants and animals, focusing on plants, microbes, or animals that exist in unusual habitats, investigating whether different plant parts and ages of plants are more likely to produce novel bioactive natural products, and biodiversity prospecting. An important primary consideration in any natural products drug discovery program, and particularly those relying on ethnobotanical or bioprospecting strategies, is the fact that the greatest biodiversity occurs in the tropical regions and the greatest ethnobotanical knowledge exists within various cultures that do not use "Western medicine," both of which often occur in developing countries. Access to the genetic property of developing countries is a complicated and sensitive matter that requires careful thought and attention to the concerns of all involved. All collections should be done as collaborative efforts with careful attention to issues of ownership of intellectual property, laws governing access to biodiversity, and political, social, and economic factors.

Initial sample size may vary, but certainly with recent advances in technology related to bioassays, isolation, dereplication, and structure elucidation, much smaller initial sample sizes are required than in the past. Initial sample size notwithstanding, attention must be given to the likelihood that additional quantities of source material will be required for promising specimens, necessitating the ability to re-collect the same specimen with confidence that similar results will be obtained with re-collected material. Once samples are acquired, voucher specimens (or type cultures, or other appropriate authenticated source material) must be maintained according to standard accepted methods and the collected specimens must be extracted or otherwise processed to prepare samples for biological evaluation. Recent developments that affect sourcing strategies include decreased access to plants and marine life, especially in developing countries. Developments that contribute to a greater range of specimens being collected and evaluated include a growing body of literature on methods to isolate, cultivate, and identify unusual microbes (slow-growing, nonabundant soil organisms, marine microbes, endophytes, etc.) and methods to collect and identify unusual marine invertebrates (Closed Circuit Underwater Breathing Apparatus, remote submersibles collecting from extreme environs, increasing taxonomic knowledge). In addition, the automation and miniaturization of extraction and bioassay techniques allows for collection of much smaller initial sample sizes, affording the opportunity to collect and evaluate specimens that were previously not accessible or sufficiently abundant. Also, improved geopositioning systems and abilities to dereplicate and structurally characterize relatively minor components (discussed later) also contribute to a diminishing demand for large initial sample sizes for screening.

There are three sources of natural products: plants, microorganisms, and animals, and there are advantages and disadvantages, opportunities and challenges associated with exploring each of these.

Plants. There are significant advantages and opportunities associated with accessing plants as a source of new drugs; there are also substantial disadvantages and challenges. Fortunately, the chemical and biological diversity of plants drives the balance in favor of advantages and opportunities, and mandates that challenges and disadvantages be addressed and overcome. Several other authors have provided excellent reviews detailing some of these benefits and concerns (1, 6–10). One of the principal advantages of plants as a source of new pharmaceuticals is that the secondary metabolism of plants appears to have evolved over centuries to retain biochemical features that guarantee chemical diversity. However, as pointed out by others (11), this does not necessarily guarantee that biological activity (especially therapeutically useful activity for humans) will also exist. In other words, just because there is chemical diversity does not mean there will be useful therapeutic activity. Nevertheless, the fact that nat-